Guidance for Industry

E2B(M): Data Elements for Transmission of Individual Case Safety Reports

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug

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ICH

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Guidance for Industry[1]
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Questions and Answers

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I. INTRODUCTION

This question and answer (Q&A) guidance is intended to assist applicants who plan the electronic transmission of individual case safety reports (ICSRs) to the Food and Drug Administration (FDA). The guidance provides answers to questions that have arisen since the finalization of the ICH E2B(M) guidance, version 4.4.1, and the M2 specification document, version 2.3. This Q&A guidance is not meant to be all inclusive, as further questions may be addressed in the future.[2] The questions and answers provided here reflect the consensus of the ICH parties.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance was developed within the E2B(M) Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, July 18, 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Further questions or comments related to the E2B(M) guidance can be submitted to: question-to-E2BM-guideline@ifpma.org .

Questions concerning the time frame or specific U.S. requirements that are not answered by the E2B(M) guidance should be addressed directly to the FDA.

Questions requiring immediate answers should be addressed directly to the FDA. It is anticipated that subsequent ICH Q&A documents will be developed and approved by the ICH Steering Committee approximately every 6 months.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The ICH guidance *E2B Data Elements for Tranmission of Individual Case Safety Reports* was signed off by the International Conference on Harmonisation (ICH) in July 1997 and issued by the FDA in January 1998. ICH subsequently issued a revised guidance, E2B(M), to provide additional information and clarification. The revised guidance incorporated adjustments based on the successful pilot projects being conducted in the three ICH regions. ICH signed off on E2B(M) in November 2001, and the FDA issued the revised guidance in April 2002.

III. QUESTIONS AND ANSWERS

Q1: During the period of transition, as health authorities or pharmaceutical companies migrate from paper to electronic ICSR submissions and exchanges using E2B(M)/M2 standards, certain ICSRs will likely be exchanged in both paper and electronic format. This could occur either because the initial ICSR was on paper and the follow-up is in electronic format or because the two parties are in a pilot program where they are exchanging ICSRs in both paper and electronic format. Two questions arise:

Question 1a: How can two or more exchanges of the same ICSR be linked together to avoid a duplicate report?

Question 1b: How can the current paper forms accommodate the full ICH format of the worldwide unique case identifier?

A1: Answer 1a: Compliant with the definition of field A.1.0.1, the ICH format of the worldwide unique case identifier (country code-company or regulator name-report number) should always be used, and copied into field A.1.10.1 or A.1.10.2. as appropriate.

In the event that the ICSR either has been exchanged by the two parties in the past using a different identifier or that it is exchanged simultaneously with a different identifier, this other identifier should be listed in field A.1.11.2 and the organization's name should be captured in field A.1.11.1, consistent with the definition of the A.1.11 field for the identification of duplicates.

This recommendation applies to DTD version 2.0 and DTD version 2.1.

Answer 1b: In case the ICH conforming worldwide unique case identifier cannot be accommodated on the paper forms, it is recommended that the report number alone (without the country code or the company or regulator name) be used.

Q2: For fields where only one MedDRA coding level is accommodated, should I use PT or LLT?

Section B.2 contains fields B.2.i.0, B.2.i.1 and B.2.i.2 to capture the verbatim term, LLT and PT, respectively. However, sections B.1.7.1a, B.1.8f, B.1.8g, B.1.9.2, B.1.9.4, B.1.10.7.1a, B.1.10.8f, B.1.10.8g, B.4.k.11, B.4.k.17.2, B.4.k.18.1, B.5.3 contain only one field and do not specify whether the LLT or PT should be used.

A2: For the ICH E2B(M) fields B.1.7.1a, B.1.8f, B.1.8g, B.1.9.2, B.1.9.4, B.1.10.7.1a, B.1.10.8f, B.1.10.8g, B.4.k.11, B.4.k.17.2, B.4.k.18.1, B.5.3 the following should be used:

- For EU regulators: LLTs
- For FDA: PTs
- For MHLW: PTs

Q3: What is the process to maintain, add, modify, or delete entries in the code lists in attachments 1 and 2 of E2B(M)?

A3: Currently these lists cannot be modified.

Q4: The current definition of B.4.k.7 calls for the use of free text until a controlled vocabulary is available. Is a harmonized vocabulary for pharmaceutical dosage forms available?

A4: There is currently no harmonized vocabulary for pharmaceutical dosage forms. Until an ICH vocabulary is available, the following should be used:

- For EU Regulators: the European Pharmacopoeia standard list
- For FDA: Free text
- For MHLW: The list of pharmaceutical forms as made available by MHLW

Q5: How can I send product-specific registration or other regulatory administrative information to multiple receivers in a single transmission?

A5: A single transmission for administrative information of an ICSR to multiple receivers in the ICH regions is currently not possible.

Various health authorities have engaged in production or pilot programs to implement E2B(M). A need to capture in more detail registration–related information (similar to the existing paper submission process using fax cover sheets or regulatory forms) became

evident. As a consequence, local guidance has been introduced to transmit additional information accompanying each ICSR:

- For EU Regulators: see E2B section B.4.k.4.
- For FDA: Field B.4.k.4.1. should contain the NDA, BLA or STN number in the appropriate format.
- For MHLW: Each ICSR should be accompanied by a corresponding J-file, as detailed in the relevant MHLW guidance documents.

Q6: What language should I use for an ICSR transmission?

A6: For EU Regulators: ICSRs in English are generally accepted. However, there can be local requirements for a translation of the case narrative in the official local language.

For FDA: English

For MHLW: Japanese

Q7: How can I submit a causality or scientific assessment in either an algorithmic or text representation in the current E2B(M) format?

A7: The current structure of E2B(M) includes fields B.4.k.18.1-4, which allow the sender to indicate such assessments for each drug-event combination.

In addition, field B.5.4 can be used to further elaborate the sender's position or assessment. Local regulatory requirements regarding expedited and periodic reporting determine whether inclusion of sponsor assessments is necessary.

Q8: How can I identify the primary source and the reporter qualification when an ICSR is forwarded by health authorities with minimal or no information on the primary source?

A8: If no information on the primary source is available, section A.2.1 should identify the health authority as the primary source. Field A.2.1.4 'Qualification' should be populated with a code of "3" (Other health professional).

In addition, field A.1.4 'Type of report' should be populated with a code of "4" (Not available to sender (unknown), if appropriate.

Q9: How can I identify the study name, the study number, the patient, and the drug in clinical trials to be reported to the EU regulators and MHLW in the E2B(M) format?

A9: The code list of 'Study type' in field A.2.3.3. is very short, so the type of study should be characterized more clearly in the study name. For a more explicit description of the study beyond 100 characters, the full study name should be given in the case narrative. In addition, some regulatory authorities request the additional submission of a regulatory study number (e.g., EUDRACT number). For this situation, the study name in element A.2.3.1 should be a concatenation of the EUDRACT number and the 'Study name', i.e., EUDRACT number-Study name.

The 'Study number' in field A.2.3.2 should be the sponsor study number.

The patient identification in a clinical trial can be transmitted in field B.1.1.1d 'Patient investigation number.' Note that multiple elements from the source database, like Center-Patient and random number, should be concatenated in this element to ensure a unique patient identification.

The trial drug identification is possible through the usual elements for the description of the suspected drug B.4.k.2.1 and B.4.k.2.2. For some countries, the project-related regulatory drug identification number can be submitted in field B.4.k.4.

The present version of E2B(M) allows for the distinction of unblinded vs. blinded information.

Q10: There may be cases where for one drug, one or more formulation/dosage, lot number and indication are provided. How should this information be presented in the electronic transmission?

A10: The drug section B.4 is a repeatable block.

If for one drug there is information on multiple dosages/formulations or indications, the entire section should be repeated to capture all the information.

For lot numbers, the guidance allows for multiple batch/lot numbers in the same field B.4.k.3. However, it is recommended that the drug section B.4 be repeated.

Q11: Field B.1.2.1 'Patient birth date' provides for population with a full date format including day, month, year. If incomplete dates are reported, how should these be presented?

A11: If an incomplete date of birth is reported, then the field B.1.2.2. 'Age at the time of onset of reaction/event' should be used, as indicated in the user guidance. Alternatively, field B.1.2.3 'Patient age group (as per reporter)' can be used to indicate the age of the patient.